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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,402	08/14/2001	Tsuneyuki Nagae	PO7336US00/LRP	8312

881 7590 02/06/2008

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EXAMINER	
CHONG, YONG SOO	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
02/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/913,402	NAGAE ET AL.	
	Examiner	Art Unit	
	Yong S. Chong	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 11/20/2007. Claim(s) 1-2 have been cancelled. Claim(s) 7-8 have been added. Claim(s) 3-8 are pending. Claim(s) 3 and 5 have been amended. Claim(s) 3-8 are examined herein.

Applicant's arguments have been fully considered but found not persuasive. The rejection(s) of the last Office Action are maintained for reasons of record and modified below as a result of Applicant's amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 3-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyamekye et al. (Circulation 1995; 91:417-425) in view of Narciso Jr., (US Patent 5,298,018), Aizaw et al. (US Patent 5,308,861), and Antoshkiw et al. (US Patent 4,471,779).

The scope of the pending claims is essentially directed to a method of performing photodynamic therapy to reduce restenosis post an angioplasty procedure comprising administering Npe6 intravenously to a patient who has undergone an angioplasty procedure and subjecting the patient at a point of 0.5-6 hours after administration of Npe6 to a local irradiation of laser light of 664 nm wavelength at laser fluence of 1-10 J/cm2. Examiner adds that the delivery process instantly described in claim 3 is inherent to the PCTA procedure and those described by the cited prior art.

For example, Narciso teaches that photodynamic therapy during PCTA procedure to limit restenosis of a blood vessel intima subject to a smooth cell proliferation (see abstract). Narciso specifically explains that the use of a photodynamic agent can be during, before or after a PCTA procedure (see col 2, lines 6-65). Narciso also suggests Npe6 to be a suitable photosensitizer for such treatment (see col 7, table 1, under class Phorobides). Since Narciso teaches the use of photodynamic therapy during a PCTA procedure, all method steps of the instant claims are also inherently disclosed.

Nyamekye teaches methods of administering photodynamic therapy to a mammal for inhibiting the development of intimal hyperplasia (restenosis) caused by a vascular intervention procedure such as balloon angioplasty (see abstract; pages 3-5).

Nyamekye clearly teaches inhibiting restenosis in vessels of rats that have undergone a balloon angioplasty and have experienced stretch injury of aorta. (see page 8-9). Such teaching meets the instant limitation of suppressing thickening of vascular intima of blood vessels.

Nyamekeye uses 5-amiono-levulinic acid as the photosensitizer and applies a laser radiation of about 50 J/cm2 at 630 nm wavelength for a period of 30-90 minutes after administration of the photosensitizer (see page 3-5, under the heading "methods and material"). Nyamekyes administers his photodynamic methodology to rats after they have undergone an angioplasty procedure. Nyamekyes suggests photodynamic therapy given at suitable time after angioplasty will eliminate the expected restenosis post an angioplasty procedure (see page 13, last paragraph).

However, Nyamekye fails to explicitly teach the use of mono-L-aspartylchlorin e6 at a laser wavelength of 667 nm and a laser density of 1 J/cm2.

Narciso teaches that photodynamic therapy is also effective during PCTA procedure to limit restenosis of a blood vessel intima subject to a smooth cell proliferation (see abstract). Narciso specifically explains that the photodynamic agent can be intravenously administered during, before or after a PCTA procedure (see col 2, lines 15-35). Narciso also suggests Npe6 to be a suitable photosensitizer for such treatment (see col 7, table 1, under class Phorobides). Narciso teaches the activation wavelength of Npe6 to be about 660 nm and describes suitable dosing (Table 1). Some photosensitizing agents are activated at much longer wavelengths, such as 660-690 nm (col. 2, lines 55-56). Narciso uses a light dose of 20 J/cm2 (see col 8, lines 63-69; col 9,

lines 19-34). Narciso teaches that the timing of light delivery following sensitization is about 32 hours and that determination of such parameter is a function of the pharmacokinetics of individual photosensitizers (see col 9, lines 1-55). Since Narcisco teaches the use of photodynamic therapy during a PCTA procedure (col. 4, lines 22-27), all method steps of the instant claims are also inherently disclosed.

Antoshkiw is merely used to show that it is known in the art of balloon catheters to inflate the balloon to totally occlude the blood vessel in order to treat various abnormalities with the blood vessel, such as arteriosclerotic blockage (col. 2, lines 1-8). Therefore, the skilled artisan would have been motivated to totally inflate the balloon catheter as deemed necessary with a reasonable expectation of success in treating arteriosclerotic blood vessels. Therefore, as a result of the blocked blood flow, the centering and proper alignment of the optical fiber is inherent.

Aizawa is merely used to show that the local administration of Npe6 during an intravascular catherization procedure is well described in the art for its therapeutic effects (see col 21, line 60-col 26, line 20). Aizawa also teaches the same doses of Npe6 to produce photosensitizing effects. Aizawa fails to specifically describe the same method during a Percutaneous Transluminal Coronary Angioplasty procedure (PCTA).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to substitute the ALA of Nyamekye with another photosensitizer such as Npe6 of Narciso and Aizawa and further improve the clinical outcome and prognosis of patients who undergo angioplasty procedures of Nyamekye.

One of ordinary skill in the art would have been motivated to use Npe6 at a laser wavelength of 667 nm and a laser density of 1 J/cm2, as taught by Narciso and Aizawa, in place of ALA in the angioplasty procedures of Nyamekye because: (1) Nyamekye, Narciso, and Aizawa teach the use of photosensitizers in angioplasty procedures; (2) they further suggest that any suitable photosensitizer would have provided the same clinical results and are viewed to be art recognized functional equivalents in preventing restenosis secondary to an angioplasty procedure; (3) optimizing the laser wavelengths and density is a matter of routine experimentation and described by Narciso a function of individual sensitizers; (4) therefore, one of ordinary skill in the art would have had a reasonable expectation of success in performing photodynamic therapy to reduce restenosis post an angioplasty procedure comprising administering Npe6 intravenously to a patient who has undergone an angioplasty procedure and subjecting the patient at a point of 0.5-6 hours after administration of Npe6 to a local irradiation of laser light of 664 nm wavelength at laser fluence of 1 J/cm2.

Response to Arguments

Applicant argues that the present invention administers the photosensitive compound a single time, whereas Narciso discloses multiple administrations. Furthermore, new claim 5 uses the transitional phrase "consisting of" to further emphasize that the claimed single photosensitizing compound administration is distinguishable from Narciso.

This is not persuasive because in the obviousness rejection, the primary reference is not Narciso. The primary reference is based on the Nyamekye reference, which teaches methods of administering photodynamic therapy by administering a single photosensitizing compound. The Narciso reference was merely used to show that Npe6 is a photosensitizing compound and is functionally equivalent to ALA.

Applicant argues that Narciso teaches exposing the photosensitizer to light anywhere from 5-18 days after a PTCA procedure. Therefore, the prior art fails to teach irradiating a photosensitizer within 0.5-6.0 hrs after administration, since Narciso teaches that at least 5 days must pass first.

This is not persuasive because again in the primary reference, Nyamekeye clearly applies laser radiation to the photosensitizer in a period of 30-90 minutes after administration.

In response to applicant's arguments against the references, one cannot show nonobviousness by attacking references individually where the rejections are based on the combination of references. See *In re Keller*, 642 F. 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that the method disclosed in Narciso is distinguishable from the claimed invention because substantially less power, 1 to 10 J/cm^2, and a different wavelength are used.

This is not persuasive because Narciso uses a dose of 20 J/cm^2 at 600 nm. While this is not 1 J/cm^2 and 664 nm, it is well within the range for optimization absent a showing that the novelty or criticality of the invention lies in the reduced power of the

laser or the specific wavelength claimed by the Applicant. Examiner disagrees that these specific parameters are unpredictable or take undue experimentation.

Therefore, it is obvious to optimize the dosage when the general range is disclosed. Generally, mere optimization of ranges will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "When the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimal or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also *In re Peterson*, 315 F. 3d at 1330, 65 USPQ 2d at 1382 "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." MPEP 2114.04.

Applicant argues that Narciso fails to teach inflating a catheter balloon at the prior angioplasty-dilated site during PDT to exert an outward force or pressure on the blood vessel so as to make obvious the total occlusion of a blood vessel via a completely inflated balloon.

This is not persuasive because at the outset, Nyamekeye teach that restenosis occurs after balloon angioplasty. Antoshkiw is merely used to show that it is known in the art of balloon catheters to inflate the balloon to totally occlude the blood vessel in order to treat various abnormalities with the blood vessel, such as arteriosclerotic blockage (col. 2, lines 1-8). Therefore, the skilled artisan would have been motivated to totally inflate the balloon catheter as deemed necessary with a reasonable expectation

of success in treating arteriosclerotic blood vessels. In this manner, the cited prior art teaches the limitation of inflating a balloon in order to totally occlude the blood vessel.

Applicant argues that the prior art teaches away from fully inflating a balloon catheter because Honye discloses that the angioplasty-dilated site is subject to dissection, tearing, and rupture in addition to the teaching by Edelman that when a balloon is overinflated, a variety of undesirable results occur, such as rupture of the tunica intima of the blood vessel.

This is not persuasive because although all of these concerns may be evident, it does not change or alter a reasonable expectation of success in the actual photodynamic therapy during PTCA procedure as taught by the cited prior art references. One of ordinary skill in the art knows that tearing and rupture of the blood vessel is a concern, therefore the skilled artisan would have been aware not to overinflate the balloon. Again, the laser radiation limitations are met in the primary reference, therefore the arguments directed to the balloon not having a optical fiber for laser irradiation in the Antoshkiw reference is not persuasive.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

YSC

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER